PREMATURE RUPTURE OF MEMBRANES

Pedro A. Poma, MD
Chicago, Illinois

The management of patients with premature rupture of membranes has changed markedly in the past several years. The basis for this is a combination of a better understanding of newborn physiology, improved neonatal care, refinements in antibiotic therapy, and the widespread use of maternal and fetal monitoring. The best outcome for both mother and infant undoubtedly reflects data based on a combination of factors, among which are gestational age survival, evidence of fetal distress, presence or absence of labor and sepsis, and of course, the cervical condition as it is related to labor-readiness.

An important recent advance is the recognition that an active observation management program is associated with less morbidity and mortality than the classic management course of delivery within 12 hours of membrane rupture. The fact that preterm premature rupture of membranes tends to recur in subsequent pregnancies offers an opportunity for prevention. Moreover, advances in perinatal and neonatal care will continue to improve the outcomes of these women and their children. (*J Natl Med Assoc.* 1996;88:27-32.)

key words: • premature rupture of the membranes • neonatal care

Premature rupture of the membranes occurs in approximately 10% of deliveries, and results in the loss of the natural protection of the fetus and intrauterine contents from bacterial invasion. Consequently, both the mother and her fetus are at greater risks for infection.[1] The longer the time between membrane rupture and delivery (defined as the latent period), the greater the risk of infection, especially if vaginal examinations are performed frequently.[1]

Premature rupture of membranes occurs more frequently among poor or single women, women who smoke, and teenagers.[2] Such women are also at greater risk for sexually transmitted diseases and a higher incidence of colonization with group B streptococcus and bacterial vaginosis.[2] Unfortunately, the absence of these risk factors does not protect a given patient from premature rupture of membranes, and the condition continues to affect women of all ages, races, and social classes.

In the absence of advanced neonatal care (in developing countries and during earlier times in this country), the overriding concern was avoidance of maternal sepsis, particularly if 12 hours had elapsed since rupture of membranes with no sign of onset labor or progression of labor. Thus, many women with premature rupture of membranes were induced or underwent cesarean sections if the latent period exceeded 12 hours, regardless of the gestational age of the fetus. These decisions often were made on the basis of departmental protocols, anecdotal remembrances, and a lack of objective data pertaining to the individual patient. Premature rupture of membranes remains a contributing factor to the high infant mortality rate (IMR) in the United States and should not be minimized in any scheme to protect women and their children.

While the overall IMR continues to decline (1990 rate of 9.2, a decrease of 6% from the 1989 rate of 9.8),[3] it remains unacceptably high, and contributes greatly to the US rank of 23rd in IMR among industrial nations.[3] Whereas only approximately 7% of deliveries are premature, they make an inordinate contribution to infant

From the Department of Obstetrics and Gynecology, Loyola University, Chicago, Illinois. Requests for reprints should be addressed to Dr Pedro A. Poma, Ravenswood Hospital Medical Ctr, Dept of Obstetrics and Gynecology, 4550 N Winchester Ave, Chicago, IL 60640-5205.

mortality in this country, accounting for 61% of the overall infant mortality rate.[4] For example, death due to disorders relating to short gestation and unspecified low birthweight were the leading causes of death in 1990. African-American women are more likely than white women to have pregnancies of short gestational length and to deliver infants of low birthweight.[3] Among African-American patients, premature rupture of membranes accounts for 38% of premature deliveries.[3] The causes of this disparity are numerous and relate, among other things, to access and quality of prenatal care. An understanding of the factors that lead to premature rupture of membranes, prevention of those factors identified as manageable, and continued improvements in neonatal care will help decrease the IMR. This article addresses the current management of premature rupture of membranes.

ETIOLOGY

Premature rupture of membranes is associated with several complications of pregnancy (ie, pregnancy-induced hypertension), especially in conditions that either increase uterine distention (ie, multiple fetuses, and hydramnios) or pressure (ie, uterine blunt trauma, and cocaine use-increased tone), or limit its expansion (ie, uterine malformations). It is also associated with incompetent cervix,[1] and amniocentesis or cordocentesis. Notwithstanding its association to these varied conditions, its direct relationship to infection has been the major concern and a focus of research in recent years.

Although several external factors are thought to cause premature rupture of membranes (ie, drop in barometric pressure, and sexual intercourse), infection appears to be the only accepted consequence of premature rupture of membranes, although the exact nature of this relationship remains unclear. Some researchers suggest that the evidence of infection within 12 hours of premature rupture of membranes indicates an antecedent infection, whereas evidence of infection after 72 hours indicates infection resulting from premature rupture of membranes.[5] Some authors emphasize that intra-amniotic infection precedes premature rupture of membranes.[6-9] At the same time, however, it is recognized that a local ascending infection may lead to a weakening of the membrane and consequently, membrane rupture. Current information about the initiation of labor suggests that it precedes from a "cascade" of different factors, the totality of which ultimately initiates labor. Some initiating factors may be endogenous and local in their effect (ie, on the chorion-decidual interphase), whereas others may be exogenous (ie, bacterial products).[10-12] In either event, when certain chemical factors are released at any stage of gestation, the cascade process starts and labor begins.

DIAGNOSIS

The presence of premature rupture of membranes is determined by various methods that detect amniotic fluid and its components. Often, premature rupture of membranes is suspected either because of a sudden rush of a slow, continuous leaking of fluid that does not look or smell like urine. When the diagnosis of premature rupture of membranes is not obvious, and it often is not, pH determination with nitrazin paper or amniotic fluid crystallization (ferning) helps establish the true nature of affairs. Other techniques include staining for fetal cells or the transabdominal injection of an indigo carmine-stained solution. Unless delivery is planned relatively soon, digital intracervical examination should be avoided because it has been shown that a threefold increase of positive amniotic cultures occurs in women who had vaginal examinations compared with those who did not (44% versus 16%).[13] A sterile speculum examination often confirms leakage of fluid, and even fetal maturity, if vermix caseosa is observed. If and when the diagnosis of premature rupture of membranes remains in doubt, repeat testing should be done, including ultrasound examinations to determine relative loss of amniotic fluid.

PREMATURE RUPTURE OF MEMBRANES AT TERM

Eighty percent of term pregnancies present in labor on admission, and 95% of women experience spontaneous labor within 48 hours of premature rupture of membranes.[14,15] However, after 24 hours of premature rupture of membranes without delivery, there is an increased risk of intrapartum fever, and after 72 hours, there is an increased risk of perinatal mortality. At admission, about 40% of women at term who are in labor have positive bacterial cultures, and this percentage increases over time.[13] The diagnosis of chorioamnionitis (fever, uterine tenderness, foul vaginal discharge, and leukocytosis) is made in approximately 5% of women 24 hours after the first post-premature rupture of membranes vaginal examination.[16] The rate of diagnosis of chorioamnionitis increases with increasing latent periods. Consequently, delaying delivery at term in the presence of premature rupture of membranes has no benefit for the fetus even though there is an increased incidence of cesarean delivery if premature rupture of membranes occurs in women with an unripe cervix.

The ripeness of the cervix plays a significant role in the management of women with premature rupture of membranes at term. Most of these women are admitted in labor or labor begins soon thereafter; less than 20% of such patients will not be in labor.[17,18] If the patient has a ripe cervix (cervix is 50% effaced, soft, dilated to 3 cm, and vertex is at least –1),[19] oxytocin stimulation often is successful, and a vaginal delivery can be expected. However, if the cervix is not ripe (Bishop's score <9),[19] the incidence of morbidity, as well as that of cesarean delivery, increases. Among nulliparas with an unripe cervix at admission, there is a sevenfold increase of anomalies of fetal heart rate (FHR) baseline, a 14-fold increase of decelerations (68.3%), and a sixfold increase in severe late decelerations (33.3%) compared with an unselected population of parturients (4.5%).[20] In addition, there is a fivefold increase in caesarean deliveries in nulliparas (19.4%) and an almost three-fold increase in caesarean deliveries in multiparas (11.1%), respectively, compared to those of similar parity but with a ripe cervix (3.9%). Dystocia (ie, failure to progress) is commonly noted as the reason for these cesarean.[17,18,20-22]

The majority of women at term presenting with premature rupture of membranes will go into labor spontaneously by the second or third day. Therefore, patient management using noninvasive evaluation methodologies for sepsis, fetal distress, and oligohydramnios may be followed to a spontaneous vaginal delivery of such women with an unripe cervix at term after a couple of days. However, it is important to remember proper patient management may include the use of antibiotics before the results of positive cultures are obtained, as infection often precedes symptoms by several hours.[16,23-27] The patient should be hydrated as this helps maintain adequate amniotic fluid volume. Amnioinfusion should be used if cord problems, abnormal FHR tracings, or septic complications are present or suspected.[28-30]

In the absence of oligohydramnios, fetal distress, or sepsis, induction should be started if labor has not begun 48 to 72 hours after admission. Under normal conditions, the physiological process of cervical ripening takes approximately 3 weeks.[31] An unripe cervix requires an average 10,000 mm Hg of uterine work to reach readiness for labor compared with only 1600 mm Hg for a ripe cervix.[31] Women who have an unripe cervix usually require long hours of oxytocin stimulation to attain cervical ripeness. Meanwhile, anxiety tends to build for the impending delivery, and this leads to an increased tendency to use vaginal examinations to determine the cervical state. Without question, such examinations and other invasive procedures should be kept to a minimum, as they often traumatize the cervix and introduce infection under the best of circumstances. The patient should be hydrated and treated with antibiotics, while the fetus is monitored continuously. Septic complications occur four times more often (12% versus 3%) after routine induction than after spontaneous labor,[22] although in every study that examined this question, similar proportions have not been found.[32-35]

PRETERM PREMATURE RUPTURE OF MEMBRANES

Several factors must be taken into account when the preterm patient presents with premature rupture of membranes. Among them are fetal pulmonary maturity, latency period, and anticipated mode of delivery. The presence of pulmonary maturity is a reasonable assumption in pregnancies of ⩾37 weeks gestational age. Amniocentesis or vaginal collection of amniotic fluid permits the determination of pulmonary maturity in pregnancies of ⩾32 weeks gestational age; however, accuracy of these examinations prior to this age is diminished. If pulmonary maturity can be documented, then management of the preterm should be the same as the term pregnancy.

With younger pregnancies (<37 weeks), the length of the latent period is not directly associated with maternal and fetal morbidity or mortality.[18,36,37] Women who deliver the youngest gestational age have the highest proportion of microorganisms and histological evidence of chorioamnionitis (at 26 weeks, 100%; at 30 weeks, 70%; and at 32 weeks, 60%).[38] Given these facts, antibiotic therapy should be administered early on. It takes approximately 1 hour for intravenous antibiotics to reach the fetal compartment.[39,40] Preterm delivery is associated with an increased risk of respiratory complications, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, and later, developmental problems.[36,37] Interestingly, an increased latent period decreases both the incidence and the severity of respiratory distress syndrome.[36,37]

On the other hand, oligohydramnios (defined as amniotic fluid index [AFI] of 5-8; severe oligohydramnios is defined as AFI <5) is associated with a poor prognosis,[35] an increased incidence of chorioamnionitis, cord problems (compression, prolapse, and entanglement),[28,35,36,38] and abruption.[40,41] All of these situations are associated with the diagnosis of fetal distress. An adequate amniotic fluid volume is associated with a reduced incidence of anomalies of FHR and decelerations and with better prognosis, especially when associ-

ated with the presence of fetal breathing movements.[42] Along with awareness about fetal risks, the benefits of prolonging the pregnancy and avoiding early delivery become more acceptable to the clinician. In general, the younger the gestational age of the pregnancy, the longer the latent period (eg, 85% of such patients with gestational age <37 weeks will be in labor 7 days after the onset of premature rupture of membranes).[14,15]

PREVIABLE PREMATURE RUPTURE OF MEMBRANES

Fetal survival decreases markedly when premature rupture of membranes occurs before 24 weeks gestational age,[43] although it must be recognized that a higher incidence of certain malformations, such as pulmonary hypoplasia (PH), also are associated with oligohydramnios. Pulmonary hypoplasia occurs in 5% of fetuses younger than 24 weeks.[44] In contrast, fetuses with normal ultrasound-determined thoracic/abdominal (T/A) ratios show normal survival rates.[43,44] Morales and Talley[45] recently reported a 40% survival rate in 94 newborns with premature rupture of membranes before 25 weeks of gestation (59% of those >500 g survived), 63% of whom had normal mental and psychomotor development at 1 year of age. Current advances in neonatology (monitoring, better understanding of the newborn physiology, cortoids, and surfactant use[45]) have not only moved the average gestational age of survival to younger and smaller fetuses, but have determined the survival of a greater proportion of them without sequelae.[43-46]

EXPECTANT MANAGEMENT

After confirming premature rupture of membranes, gestational age must be established or confirmed by the most accurate means possible. The presence or absence of labor and sepsis or fetal distress should also be determined and treated appropriately for the gestational age. Patients should be hydrated and given antibiotics; fetal monitoring should be used. Approximately 96.5% of fetuses 32 weeks of gestation and older demonstrate lung maturity and viability and survive.[46] Although avoidance of delivery assures a better prognosis (especially in younger pregnancies and when the cervix is not favorable for vaginal delivery), if 72 hours has elapsed without signs of labor progression, at term, induction of labor should be initiated. Remember that the unripe cervix requires longer induction. The possibility of good fetal outcome decreases <30 weeks of gestation and only 90.6% survive.[46] Hence, there is much benefit from longer intrauterine life.

Although a few preterm premature rupture of membranes pregnancies reach maturity, only 25% remained undelivered after 2 weeks.[43,44] The uterus is still the best incubator; through careful monitoring for complications related to sepsis, decreased amniotic fluid volume, and fetal distress, delivery may be postponed long enough to enhance fetal lung development and viability.

The stabilized, undelivered patient will require not only pelvic rest (no vaginal examinations, no intercourse, and no douches), but also oral temperature and pulse determinations four times a day; fetal movement counts daily; and white blood cell counts and nonstress tests twice weekly as well as weekly ultrasound (to determine fetal growth, AFI, and fetal breathing movements) and sterile speculum examinations. Whether the patient requires inhospital care or should be managed at home must be based on individual assessment.[43,44] Patients considered capable of in-home care should be well informed of the risks and prognosis associated with their condition; their prognosis is directly related to their ability to cooperate and comply with medical recommendations. The medical care team should be aware of the support services and resources available to them at home and the patients, likewise, should be informed of the facilities available through the hospital.

Early antibiotic use prolongs pregnancies and improves results for both mother and newborns. The benefits of tocolytics (as well as phenobarbital and vitamin K)[56] are not yet as clear. Some reports show benefits[44,47]; others do not. Recently, however, the use of corticoids have been accepted as beneficial. Surfactant prophylaxis or therapy improves the outcome of premature infants.[45,47]

PREVENTION

Because premature rupture of membranes tends to recur in subsequent pregnancies,[48,49] correctable factors associated with premature rupture of membranes should be modified before patients attempt another pregnancy.[48] Women who have experienced a pregnancy that includes premature rupture of membranes should be identified and closely monitored. Antibiotic therapy should be used prior to pregnancy in these women, and even administered to their sex partners, in an attempt to avoid infection during pregnancy. Several studies show longer pregnancies, larger fetuses, and decreased morbidity following the use of adequate antibiotics (compared with the index pregnancies).[48,50-54] Socioeconomic factors, namely poverty, associated poor nutrition, poor schooling, poor housing, hopelessness, inadequate access to medical care, disregard for positive lifestyles, and even

fatalism also significantly influence IMR. Premature deliveries or small-for-date newborns represent the most significant factor associated with mortality. Solutions that address the societal factors that lead to increased risk of premature rupture of membranes must be adopted if adequate medical measures are to have a positive impact on reducing the IMR.

SUMMARY

Expectant management with adequate therapy prolongs early pregnancies. Better results with less incidence of maternal and fetal morbidity and a decreased caesarean rate are reported. Even at term, the possibility of oligohydramnios, sepsis, and fetal distress should be promptly treated; the influence of an unripe cervix is significant. Management should be tailored to the individual patient.

Literature Cited

1. American College of Obstetricians and Gynecologists. Premature rupture of the membranes. *Technical Bulletin.* April 1985, no. 115.

2. Martius J, Krohn MA, Hillier SL, Stamm WE, Holmes KK, Eschenbach DA. Relationship of vaginal lactobacillus species, cervical chlamydia trachomatis, and bacterial vaginosis to preterm birth. *Obstet Gynecol.* 1988;71:89-95.

3. Infant mortality—United States 1990. *JAMA* 1993;-269:1616-1618.

4. Kempe A, Wise PH, Barkan SE, Sappenfield WM, Sachs B, Gortmaker SL, et al. Clinical determinants of racial disparity in very low birth weight. *N Engl J Med.* 1992;327:969-973.

5. Johnson JWC, Barnes AC. Premature rupture of the membranes: 14 years experience. *J Reprod Med.* 1985; 30:841-848.

6. Miller JM Jr, Pupkin MJ, Hill GB. Bacterial colonization from amniotic fluid with intact fetal membranes. *Am J Obstet Gynecol.* 1980;136:796-804.

7. Minkoff H. Prematurity: infection as an etiologic factor. *Obstet Gynecol.* 1983;62:137-144.

8. Toth M, Witkin SS, Ledger W, Thaler H. The role of infection in the etiology of preterm birth. *Obstet Gynecol.* 1988;71:723-726.

9. Romen Y, Greenspoon J, Artal R. Clinical chorioamnionitis: analysis of the incubation period in patients with preterm premature rupture of membranes. *Am J Perinatol.* 1985;2:314-316.

10. Romero R, Hobbins JC, Mitchell MD. Endoxin stimulates Proglandin E_2 production by human amnion. *Obstet Gynecol.* 1988;71:227-228.

11. Romero R, Brody DT, Oyarzum E, Mazor M, Wu YK, Hobbins JC, et al. Infection and labor, III: interleukin-1: a signal for the onset of parturition. *Am J Obstet Gynecol.* 1989;160:1117-1123.

12. Cunningham FG, McDonald PC, Gant NF. *Parturition: Biomolecular and Physiologic Processes. Williams Obstetrics.* 18th ed. East Norwalk, Conn: Appleton & Lange; 1989.

13. Lewis DF, Major CA, Towers CV, Asrat T, Harding JA, Garite TJ. Effects of digital vaginal examinations on latency period in preterm rupture of membranes. *Obstet Gynecol.* 1992;80:630-634.

14. Hauth JC, Gilstrap LC III, Hankins GDV. Term maternal and neonatal complications of acute chorioamnionitis. *Obstet Gynecol.* 1985;66:59-62.

15. Wilson JC, Levy DL, Wilds PL. Premature rupture of membranes prior to term: consequences of non-intervention. *Obstet Gynecol.* 1982;60:601-606.

16. Newton ER, Prihoda TJ, Gibbs RS. Logistics regression analysis of risk factors for intra-amniotic infection. *Obstet Gynecol.* 1989;73:571-575.

17. Duff P, Huff RW, Gibbs RS. Management of premature rupture of the membranes and unfavorable cervix in term pregnancy. *Obstet Gynecol.* 1984;63:697-702.

18. Kappy KA, Cetrulo CL, Knuppel RA, Ingardia CJ, Scerbo JC, Mitchell GW. Premature rupture of membranes: a conservative approach. *Am J Obstet Gynecol.* 1979;134:655-661.

19. Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol.* 1964;24:266-268.

20. Hydstrom H, Arulkumaran S, Ingemasson I, Kumar KJ, Ratman SS. Premature rupture of the membranes at term: obstetrical outcome with oxytocin stimulation in relation to parity and cervical dilation at admission. *Acta Obstet Scand.* 1986;65:587-591.

21. Kappy KA, Cetrulo CL, Knuppel RA. Premature rupture of the membranes at term. *J Reprod Med.* 1982;27:29-33.

22. Morales WJ, Lazar AJ. Expectant management of rupture of membranes at term. *South Med J.* 1986;79:955-958.

23. Monif GRG, Hume R, Goodline RC. Neonatal consideration in the management of premature rupture of fetal membranes. *Obstet Gynecol Surv.* 1986;41:531-537.

24. Gilstrap LC, Leveno KJ, Cox SM, Burris JS, Mashburn M, Rosenfeld CR. Intrapartum treatment of acute chorioamnionitis: impact on neonatal sepsis. *Am J Obstet Gynecol.* 1988;159:579-583.

25. Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. *Obstet Gynecol.* 1988;72:823-828.

26. Gibbs RS, Duff P. Progress in the pathogenesis and management of clinical intra-amniotic infection. *Am J Obstet Gynecol.* 1991;164:1317-1326.

27. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotic and the risk of surgical wound infection. *N Engl J Med.* 1992;326:281-286.

28. Imanaka M, Ogita S, Sugawa T. Saline solution amnioinfusion for oligohydramnios after premature rupture of membranes. *Am J Obstet Gynecol.* 1989;161:102-106.

29. Schrimmer DB, Macri CJ, Paul RH. Prophylactic amnioinfusion as a treatment for oligohydramnios in laboring patients: a prospective, randomized trial. *Am J Obstet Gynecol.* 1991;165:172-175.

30. Owens J, Henson BV, Hauth JC. A prospective randomized study of saline solution amnioinfusion. *Am J Obstet Gynecol.* 1990;162:1146-1149.

31. Cibils LA. Normal uterine contractility. In: Wright J, ed. *Electronic Fetal-Maternal Monitoring.* London, England: PSG Inc; 1981:64-110.

32. Wagner MV, Chin VP, Peters CJ, Drexler B, Newman LA. A comparison of early and delayed induction of labor with

spontaneous rupture of membranes at term. *Obstet Gynecol.* 1989;74:93-97.

33. Rydhstrom H, Ingermarsson I. No benefit from conservative management in nulliparous women with premature rupture of membranes at term. A randomized study. *Acta Obstet Gynecol Scand.* 1991;70:543-547.

34. Grant JM, Serle E, Mahmood T, Sarmadal P, Conway DI. Management of prelabor rupture of the membranes in term primigravida: report of a randomized prospective trial. *Br J Obstet Gynecol.* 1992;99:557-562.

35. Kilpatrick SJ, Safford KL, Pomeroy T, Hoeat L, Scheerer L, Laros RK. Maternal hydration increases amniotic fluid index. *Obstet Gynecol.* 1991;78:1098-1102.

36. Beydoun SN, Yasin SY. Premature rupture of membranes before 28 weeks: conservative management. *Am J Obstet Gynecol.* 1986;155:471-479.

37. Druzin ML, Toth M, Ledger WJ. Nonintervention in premature rupture of the amniotic membranes. *Surg Gynecol Obstet.* 1986;163:5-10.

38. Hillier SL, Martins J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamniotic infection and histologic chorioamnionitis in prematurity. *N Engl J Med.* 1988;31:972-978.

39. Kirschbaum T. Antibiotics in the treatment of preterm labor. *Am J Obstet Gynecol.* 1993;168:1239-1246.

40. De Leeuw JW, Roumen FJME, Bouckaert PXJM, Cremers HMHG, Vree TB. Achievement of therapeutic concentrations of cefuroxime in early preterm gestations with premature rupture of the membranes. *Obstet Gynecol.* 1993;81:255-260.

41. Darby MJ, Caritis SN, Shen-Schwarz S. Placental abruption in the preterm gestation: an association with chorioamnionitis. *Obstet Gynecol.* 1989;74:88-92.

42. Saftlas AF, Olson DR, Atrash HK, Rochat R, Rowley D. National trends in the incidence of abruptio placentae, 1979-1987. *Obstet Gynecol.* 1991;78:1081-1086.

43. Vintzileos AM, Campbell WA, Nochinmson DJ, Weinbaum PJ. Fetal breathing as a predictor of infection in premature rupture of the membranes. *Obstet Gynecol.* 1986;67:813-817.

44. Bengtson JM, Van Marter LJ, Barass VA, Greene MF, Tuomala RE, Epstein MF. Pregnancy outcome after premature rupture of the membranes at or before 26 weeks' gestation. *Obstet Gynecol.* 1989;73:921-926.

45. Morales WJ, Talley T. Premature rupture of the membranes at less than 25 weeks: a management dilemma. *Am J Obstet Gynecol.* 1993;168:503-507.

46. Long W, Corbet A, Cotton R, Courtnet S, McGuiness G, Walter D, et al. The American and the Canadian Exosurf Neonatal Study Group. A controlled trial of synthetic surfactant in infants weighing 1250 gm or more with respiratory distress syndrome. *N Engl J Med.* 1991;325:1696-1703.

47. Copper RL, Goldenberg RL, Creasey RK, Du Bard MB, Davis RO, Entman SS, et al. A multicenter study of preterm birth weight and gestational age-specific neonatal mortality. *Am J Obstet Gynecol.* 1993;168:78-84.

48. Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. *Am J Obstet Gynecol.* 1993; 168:508-513.

49. Asrat T, Lewis DF, Garite TJ, Major GA, Nageotte MP, Towers CV, et al. Frequency of recurrence of preterm premature rupture of membranes. Presented at the XI Annual Meeting of the Society of Perinatal Obstetricians, 1991.

50. Amon E, Lewis SV, Sibai BM, Villar MA, Arheart KL. Ampicillin prophylaxis in preterm premature rupture of the membranes: a perspective, randomized study. *Am J Obstet Gynecol.* 1988;159:539-543.

51. Johnston MM, Sanchez-Ramos L, Vaughn AJ, Todd NW, Benrubi GI. Antibiotic therapy in preterm rupture of membranes. A randomized, prospective, double-blind trial. *Am J Obstet Gynecol.* 1990;163:743-747.

52. McGregor JA, French JI, Seo K. Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 1991;165:867-875.

53. Christmas JT, Cox SM, Andrews W, Dax J, Leveno KJ, Gilstrap LC. Expectant management of preterm ruptured membranes: effects of antimicrobial therapy. *Am J Obstet Gynecol.* 1992;80:759-762.

54. Romero R, Hagay Z, Nores J, Sepulveda W, Mazor M. Eradication of ureaplasma urealyticum from the amniotic fluid with transplacental antibiotic treatments. *Am J Obstet Gynecol.* 1992;166:618-620.